An acute study of the electrophysiological and haemodynamic effects of intravenous UK-52,046, a novel α_1 -adrenoceptor antagonist

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The acute electrophysiological and haemodynamic effects of UK-52,046, a novel α_1 -adrenoceptor antagonist ($0.5 \mu\text{g kg}^{-1}$) were studied in 10 patients. Resting and paced conduction intervals, refractory periods, Wenckebach cycle length and sinus node recovery time were measured and compared with baseline values. Haemodynamic measurements including cardiac output were measured before and after drug administration. Changes in QRS interval (83 to 105 ms) and QRS duration during sinus rhythm (83 to 105 ms) or during constant atrial pacing (85 to 109 ms), were not significant ($P > 0.05$). Myocardial refractoriness and sinus node recovery time were not altered by the drug. Slight increases in mean heart rate (72.5 to 78.8 beats min^{-1}), mean right atrial pressure (4.5 to 5.5 mm Hg) and mean cardiac output (5.4 l min^{-1} to 5.7 l min^{-1}), were not significant ($P > 0.05$). Systolic and diastolic arterial pressure, cardiac work indices, and vascular resistance remained unchanged. These results demonstrate the safety of this drug given intravenously in a non-ischaemic setting, and warrant its further investigation as an antiarrhythmic agent in myocardial ischaemia.

Keywords electrophysiology haemodynamic α_1 -adrenoceptor antagonist

Introduction

Cardiac α_1 -adrenoceptors play a major role in the pathogenesis of ischaemia-induced arrhythmias (Sheridan *et al.*, 1980). Antagonists to these receptors have been shown capable of restoring sinus rhythm after experimentally induced arrhythmias, but their clinical use has been hampered by the hypotensive effects of these compounds (Sheridan *et al.*, 1980).

A new agent, UK-52,046 (4-amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinol-2-yl) quinoline methanesulphonate), is a potent α_1 -adrenoceptor antagonist which shows little vasodilator activity in doses which are antiarrhythmic in experimentally induced ischaemia (Aubrey *et al.*, 1988; Uprichard *et al.*, 1988). The purpose of this study, which was

performed in a non-ischaemic setting, was to examine the acute electrophysiological and haemodynamic effects of UK-52,046 given intravenously in man.

Methods

Patients undergoing routine angiography or electrophysiological studies were eligible for the study. Informed Ethics Committee approved written witnessed consent was obtained from each subject prior to the study. Patients with heart failure, severe valvular heart disease, recent (< 3 months) myocardial infarction, unstable angina pectoris, severe coronary artery

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disease, or hypertension were excluded. No patient had established atrial flutter or fibrillation. All cardiac medications were suspended at least 24 h prior to the investigation.

Baseline measurements

Blood samples for serum biochemistry and haematology were obtained before the study, as was a 12-lead surface electrocardiogram (ECG). Baseline supine, sitting and standing blood pressures, with corresponding heart rates were obtained by cuff sphygmomanometer prior to each study. Urine was examined by dipstick analysis.

Catheterisation procedures

The femoral vein was cannulated following local anaesthesia for passage of six French gauge electrode catheters under direct fluoroscopy. A quadripolar catheter was placed at the right ventricular apex, another in the high right atrium, and a tripolar electrode was placed at the atrioventricular junction to record His bundle electrocardiograms. In patients who had undergone prior coronary arteriography, an arterial sheath was used for pressure recording during drug administration. A balloon-tipped (Swan-Ganz) thermodilution catheter was used to record right atrial, pulmonary artery and pulmonary wedge pressures, in addition to cardiac output.

Study protocol

The pre-dose baseline electrophysiological parameters measured were: sinus cycle length (SCL), PA interval, AH interval, HV interval, QRS duration, and QT interval (absolute and corrected QT_c). Intervals measured during atrial pacing were: atrial effective refractory period (AERP), atrio-ventricular node functional refractory period (AVFRP), atrio-ventricular effective refractory period (AVERP), and atrial Wenckebach cycle length (AWCL). Intervals measured during ventricular pacing were: ventricular effective refractory period (VERP), ventriculo-atrial effective refractory periods (VAERP), and ventricular Wenckebach cycle length (VWCL). Sinus node function recovery was assessed by high right atrial pacing for 15, 30 and 60 s at drive cycle lengths of 600, 500 and 400 ms. All intervals were measured to the nearest 5 ms. Sinus node recovery time was expressed as the maximum absolute duration (SNRT), and the maximum value corrected for heart rate (SNRT_c).

Right-sided intracardiac pressures, and cardiac output in triplicate were obtained prior to the dose of drug. These measurements were repeated 10 min after the end of drug infusion, following which the electrophysiological parameters were measured again.

The drug was administered as the mesylate salt in a solution containing 25 µg base ml⁻¹, in a dose of 0.5 µg kg⁻¹ infused over 2 min into an antecubital vein.

Following completion of the invasive study, blood pressure and heart rate were monitored for up to 8 h. A 12-lead surface ECG was repeated at 24 h, and further blood samples were obtained for clinical chemistry and haematology. Urine was checked for abnormalities by dipstick. Any side effects observed or reported during the study period were to be recorded.

Statistical analysis

Results were compared using Student's *t*-test, and one-way analysis of variance for repeated measures. Differences were considered significant at *P* < 0.05.

Results

Eight male and two female subjects were studied (mean age 51 ± 5.4 years, range 44–59). The diagnosis at presentation was Wolff-Parkinson-White (WPW) syndrome in three patients, one of whom had documented episodes of atrial fibrillation in addition to AV re-entrant tachycardia. No patient had critical coronary occlusive disease. One male patient with presyncope had sinus bradycardia at the time of the procedure.

Drug administration was well tolerated in every case, with no side effects reported for the 8 h observation period. The electrophysiological and haemodynamic parameters comparing baseline and following drug infusion measurements are summarised in Table 1. PR, QRS and QT intervals from patients with WPW syndrome were excluded from analysis, as these intervals are not valid in the presence of pre-excitation. There were no significant differences in resting or dynamic electrophysiological data before and after drug. No significant changes were observed in any blood or urine parameter measured before and after drug administration.

Discussion

This study shows that the selective α₁-adrenoceptor antagonist UK-52,046 has no significant electrophysiological effects when administered

Table 1 Baseline and post drug electrophysiological intervals, pacing parameters and haemodynamic parameters (mean $\pm$ s.e. mean)

	Baseline	Post drug	Significance
SCL (ms)	883 $\pm$ 78	785 $\pm$ 64	NS
AH (ms)	86 $\pm$ 9	87 $\pm$ 10	NS
HV (ms)	43 $\pm$ 5	40 $\pm$ 5	NS
QRS* (ms)	83 $\pm$ 8	105 $\pm$ 29	NS
QT* (ms)	364 $\pm$ 7	357 $\pm$ 7	NS
QT _c (ms)	394 $\pm$ 14	409 $\pm$ 11	NS
PCL (ms)	580 $\pm$ 20	580 $\pm$ 20	NS
PA (ms)	59 $\pm$ 7	54 $\pm$ 6	NS
AH _p (ms)	114 $\pm$ 18	99 $\pm$ 12	NS
HV _p (ms)	43 $\pm$ 5	41 $\pm$ 6	NS
QRS _p (ms)	85 $\pm$ 8	109 $\pm$ 29	NS
QT _p * (ms)	351 $\pm$ 7	350 $\pm$ 8	NS
AVFRP (ms)	516 $\pm$ 16	486 $\pm$ 13	NS
AVRP (ms)	333 $\pm$ 21	313 $\pm$ 28	NS
AVERP (ms)	242 $\pm$ 10	227 $\pm$ 11	NS
VAERP (ms)	301 $\pm$ 29	277 $\pm$ 29	NS
VERP (ms)	250 $\pm$ 17	233 $\pm$ 19	NS
AWCL (ms)	399 $\pm$ 10	393 $\pm$ 28	NS
VWCL (ms)	348 $\pm$ 21	291 $\pm$ 17	NS
SNRT _{max} (ms)	1323 $\pm$ 196	1300 $\pm$ 282	NS
SNRT _c (ms)	487 $\pm$ 160	528 $\pm$ 227	NS
SBP (mm Hg)	123 $\pm$ 6	123 $\pm$ 7	NS
DBP (mm Hg)	77 $\pm$ 4	76 $\pm$ 5	NS
MAP (mm Hg)	92 $\pm$ 4	92 $\pm$ 5	NS
HR (beats min ⁻¹)	72.5 $\pm$ 4.4	78.8 $\pm$ 5.4	NS
RAP (mm Hg)	4.5 $\pm$ 0.1	5.5 $\pm$ 0.9	NS
PAS (mm Hg)	24.2 $\pm$ 1.5	22.8 $\pm$ 1.4	NS
PAD (mm Hg)	10.8 $\pm$ 0.9	10.7 $\pm$ 1	NS
PAM (mm Hg)	15.3 $\pm$ 0.8	14.4 $\pm$ 1.1	NS
PACW (mm Hg)	7.7 $\pm$ 0.9	7.0 $\pm$ 0.8	NS
CO (l min ⁻¹)	5.4 $\pm$ 0.4	5.7 $\pm$ 0.5	NS
CI (l min ⁻¹ m ⁻²)	2.8 $\pm$ 0.3	3.0 $\pm$ 0.3	NS
SV (ml)	75.7 $\pm$ 6.8	76.3 $\pm$ 8.3	NS
SVI (ml m ⁻²)	39.7 $\pm$ 3.5	39.8 $\pm$ 4.1	NS
SWI (ml mm Hg m ⁻²)	45.8 $\pm$ 4.8	46.2 $\pm$ 5.6	NS
SVR (dyn s cm ⁻⁵)	1386 $\pm$ 138	1207 $\pm$ 124	NS
PVR (dyn s cm ⁻⁵)	114 $\pm$ 11	103 $\pm$ 11	NS

Abbreviations: SCL, sinus cycle length (ms); p, paced intervals; *, interval measurements exclude patients with Wolff-Parkinson-White Syndrome; AVFRP, atrioventricular functional refractory period; AVERP, atrioventricular effective refractory period; AERP, atrial effective refractory period; VAERP, ventriculo-atrial effective refractory period; VERP, ventricular effective refractory period; AWCL, atrial Wenckebach cycle length; VWCL, ventricular Wenckebach cycle length; SNRT_{max}, maximum sinus node recovery time; SNRT_c, corrected sinus node recovery time (maximum); SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure; PAS, pulmonary artery systolic pressure; PAD, pulmonary artery diastolic pressure; PAM, pulmonary artery mean pressure; PACW, pulmonary artery wedge pressure; CO, cardiac output; CI, cardiac index; SV, stroke volume; SVI, stroke volume index; SWI, stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; NS, not significant.

to patients without significant coronary artery disease, and causes no significant supine haemodynamic effects at the study dose of $0.5 \mu\text{g kg}^{-1}$. Studies in volunteers have shown (Shafers *et al.*, 1989) that a single intravenous dose of $0.5 \mu\text{g kg}^{-1}$ produces α -adrenoceptor blockade for up to 12 h after dosing and that this effect is related to circulating drug levels (Miller *et al.*, 1989). The electrophysiological safety of this compound has not been previously documented in man, whereas the haemodynamic findings are in accord with findings in experimental animals (Flores & Sheridan, 1989; Uprichard *et al.*, 1988) and in man (Harron *et al.*, 1989; McKaigue *et al.*, 1989; Miller *et al.*, 1989).

In an experimental model (Aubry *et al.*, 1988), intravenous UK-52,046 caused an elevation of the threshold for adrenaline induced arrhythmias, at no cost to haemodynamic parameters such as heart rate, blood pressure or filling pressure. Mild clinically insignificant postural effects have been seen in volunteers after intravenous doses up to $0.8 \mu\text{g kg}^{-1}$ (Harron *et al.*, 1989; Schafers, 1989), in contrast to prazosin (McKaigue *et al.*, 1989; Tomlinson *et al.*, 1989). We were unable to assess postural effects in this study because of the nature of the invasive cardiac investigations which required supine recovery, however, we could detect no change in recumbent pressures both acutely and

for up to 8 h following drug administration, consistent with the findings of a recent study in man (Schafers *et al.*, 1989).

Most deaths immediately following acute myocardial infarction are related to ventricular arrhythmias (Moss, 1982), perhaps due to profound alterations in autonomic nervous function (Barber *et al.*, 1983). In this setting of increased sympathetic activity and enhanced catecholamine release, cardiac α_1 -adrenoceptors appear to play a primary role in the pathogenesis of ischaemia-induced ventricular arrhythmias (Sheridan *et al.*, 1980). Selective α -adrenoceptor blockade may prevent these arrhythmias. Compared with prazosin, UK-52,046 shows little vasodilator activity at equivalent antiarrhythmic doses during ischaemia during experimental coronary occlusion (Aubry *et al.*, 1988; Flores & Sheridan, 1989). Therefore, this compound shows potential as a haemodynamically safe antiarrhythmic drug.

Our observation that no significant electrophysiological changes occurred is consistent with similar observations in studies with prazosin and β -adrenoceptor blockers. However, these findings are only limited to the non-ischaemic setting. As it is known that cellular conduction alters markedly during ischaemia, the precise effect of UK-52,046 in this setting remains to be elucidated.

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